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OPEN

Primary Cardiac Allograft Dysfunction—Validation of a Clinical Definition

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Background. Heart transplantation is an established treatment for advanced heart failure. Primary allograft dysfunction (PGD) is reported in up to 40% of transplants and is associated with a poor outcome. **Methods.** As part of Heart Evaluation and Retrieval for Transplantation study, an investigation of the assessment of donor hearts for transplantation, we proposed a clinical definition for cardiac PGD comprising severely impaired systolic function affecting one or both ventricles accompanied by hypotension, low cardiac output, and high filling pressures occurring in the first 72 hours (in the absence of hyper acute rejection and technical surgical factors, such as cardiac tamponade). Here, we examine the prospective application of this definition to 290 heart transplants. We compared the clinical outcome of PGD and non-PGD cases. **Results.** Ninety-four of 290 transplants developed PGD (32.4%). Inotrope use (score) was higher in the PGD group at 24, 48, and 72 hours after transplantation ($P < 0.01$). In the PGD group, there was a greater requirement for, intra-aortic balloon pump (50% vs 15%, $P < 0.01$), mechanical support (27% vs 0%, $P < 0.01$), and renal replacement therapy (61% vs 26%, $P < 0.01$). Intensive care stay was longer for recipients with PGD (median 14 vs 5 days, $P < 0.01$) and early mortality was higher (37% vs 4% at 30 days, 42% vs 8% at 1 year, $P < 0.01$). **Conclusions.** In conclusion, our definition of PGD could be applied in a national multicenter study, and the cases it defined had more frequent complications and higher mortality.

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Heart transplantation is a recognized treatment for advanced heart failure improving survival and quality of life.[1-4] Survival after transplantation has improved from 1 week after the first procedure in 1967 to a median of over 10 years,[5] and some patients have now survived over 30 years.[6] This has been attributed to improvements in donor management,[7,8] organ preservation techniques,[9] pharmacological immunosuppression,[10-12] and diagnosis of rejection.[13]

Postoperative cardiac allograft dysfunction may result in a low cardiac output (CO) syndrome requiring prolonged inotropic or mechanical circulatory support and possible retransplantation.[14] In the absence of an alloimmune response or technical issue affecting the transplant, this is described as primary allograft dysfunction (PGD), and more severe cases, resulting in death, are described as primary graft failure (PGF).

The PGD remains an important problem after heart transplantation; it is reported to have an incidence up to 40%[15–21] and is responsible for up to 40%, of deaths within 30 days,[16,22,23] and 18% of deaths between 31 days and 1 year after transplantation.[16,19,24] The variation in incidence between studies may be partly due to the lack of a standardised definition of PGD.

The occurrence of PGD in donor hearts that appeared to have acceptable function before organ retrieval may be explained by the cumulative effect of a series of injuries associated with retrieval, transportation, and during and after implantation. Brain stem death in the donor affects cardiac function by mechanisms that include the catecholamine storm[25,26] and hemodynamic changes that cause myocardial stress, particularly transient severe hypertension. These effects are compounded by subsequent hypotension, reduced coronary perfusion, the therapeutic use of exogenous catecholamines, and an evolving proinflammatory milieu.[25,27–31] Although the impact of

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myocardial ischemia during organ retrieval is reduced by cardioplegic cardiac arrest and cooling, myocardial injury and dysfunction still develop in a time-dependant fashion.[19,22,32] Further injury occurs during implant surgery, especially during cardiac reperfusion, followed by the impact of an innate immune response in the recipient.[33,34]

Although PGF represents the lethal form of PGD, PGD may also lead to death indirectly through secondary organ failure or complications of therapy. Multiorgan failure and renal failure cause 14% and 0.6% of deaths within 30 days of transplantation, respectively, and both may be a consequence of PGD.[24] In addition, some PGD deaths may be misclassified as being due to right heart failure secondary to recipient pulmonary hypertension.[23,35–39] Consequently, the magnitude of the impact of PGD on the outcome of heart transplantation remains poorly defined.

The purpose of this study was to evaluate in a prospective manner the use of a proposed definition of PGD based on clinical parameters in the first 72 hours after transplantation.

MATERIALS AND METHODS

As part of a United Kingdom-based prospective study, funded by the British Heart Foundation, titled the Heart Evaluation And Retrieval for Transplantation (HEART) study, clinical and physiological data from consecutive donors of transplanted hearts and the corresponding recipients were collected from March 2007 to November 2011. The study had received ethics approval from a national multicenter research ethics committee Scotland (ref 05/MRE00/66).

Consent for the study was sought from the next of kin, and donor data were collected prospectively by the donor transplant co-ordinators for NHS Blood and Transplant, where data were compiled and validated before forwarding to our study center. Recipient data were collected by recipient transplant co-ordinators at each of the 6 U.K. heart transplant centers. We defined PGD as "A severe impairment of systolic graft function affecting the right, left, or both ventricles accompanied by hypotension, low CO, and high filling pressures, that is, pulmonary capillary wedge pressure (PCWP) greater than 18 mm Hg or a more than 30% increase in PCWP and a cardiac index (CI) less than 2.5 L/min per m^2 or more than 30% decrease in CI within the first 72 hours", in the absence of technical complications, (including tamponade) and hyper acute rejection.

After applying this definition to the national cohort of heart transplants, we validated it against the clinical outcome of the transplant; including recipient inotrope requirements, the need for an intra-aortic balloon pump (IABP) or other mechanical circulatory support and also evaluated its consequences in terms of need for renal replacement therapy, length of intensive care unit stay, and mortality at 30 days 1 year, and 3 years.

Data were summarized as mean and standard deviation (SD) or median and interquartile range, as appropriate. Transplants with and without PGD were compared using the Student *t* test or the Wilcoxon test, as appropriate. Binary outcomes were assessed using the χ^2 test or Fisher exact test if expected frequencies were less than 5, and time to event outcomes were analyzed using survival methods and evaluated using a log rank test. For length of stay, patients who died before hospital discharge were treated as censored observations. Inotrope scores were compared by fitting a generalized linear model which allowed for the correlation between scores measured at repeated time points after transplantation. The inotrope scores were highly skewed and a γ model with reciprocal link provided the best fit to the data (after excluding 2 extreme outlying values).

Drugs dosages were converted to μg/kg per minute to calculate an inotrope score. This was defined as: "Dopamine (dose × 1) + Dobutamine (dose × 1) + Amrinone (dose-1) + Milrinone (dose × 15) + Epinephrine (dose-100) + Norepinephrine (dose × 100) + Enoximone (dose × 1) + Isoprenaline (dose × 100)".[40–43]

At a recent consensus group meeting on PGD at the 2013 International Society for Heart and Lung Transplantation annual meeting in Montreal, a definition of PGD and its grading was proposed.[44] Therefore, we attempted to retrospectively classify our PGD cases according to the proposed grades and examine the survival by PGD grade. Three PGD grades were proposed based on left ventricular function. Mild PGD (grade 1); left ventricular ejection fraction (LVEF) 40% or lower or hemodynamics with right atrial (RA) pressure greater than 15 mm Hg, PCWP less than 20 mm Hg, CI less than 2.0 L/minute per m^2 (>1 hr) and low-dose inotropes (score < 10). Moderate PGD (grade 2); LVEF 40% or lower and hemodynamics with RA greater than 15 mm Hg, PCWP greater than 20 mm Hg, CI less than 2.0(>1 hour) plus inotrope score 10 or higher, or newly placed IABP. Severe PGD (grade 3); dependant on left or biventricular mechanical support including extra corporeal membrane oxygenation (ECMO), left ventricular assist device, biventricular assist device or percutaneous left ventricular assist device except IABP.

To apply a similar grading system to our study data, we considered the requirement for IABP, VAD, and ECMO and calculated the inotrope score in the first 72 hours after transplantation. We had prospectively collected inotrope usage, and 6, 24, 48, and 72 hours after transplantation, this allowed us to calculate an inotrope score at each time point. Using this score and the utilization of IABP, VAD, ECMO, we divided our PGD cohort into grades 2 and 3, based on the inotrope scores and mechanical support as outlined in the PGD-Primary allograft dysfunction-The International Society for Heart and Lung Transplantation (PGD-ISHLT) definition, but over the first 72 hours after transplantation instead of just 24 hours.

RESULTS

A total of 528 transplants in 520 recipients were performed using hearts from adult donors (aged 16 years or older) during the study period. Of these 528 transplants, donor family consent for the study was given for 314 (59%) (Figure 1), data were not submitted for 11 of these hearts, 10 were transplanted as heart lung blocks, and 3 were a second transplantation carried out within 72 hours of the first; these second heart transplantations were excluded. For the 3 recipients of 2 hearts within 72 hours, the first transplant was considered to have PGD and the recipient classified as having developed PGD regardless of the outcome of the second heart. Of the 301 heart only transplants in the study cohort, 8 were second transplants, the recipients having received their first transplant before the study started (time from first to second transplant ranged from 66 to 2758 days); these were included in the study. Centres classified the recipient as having developed PGD using our prespecified definition, and this was

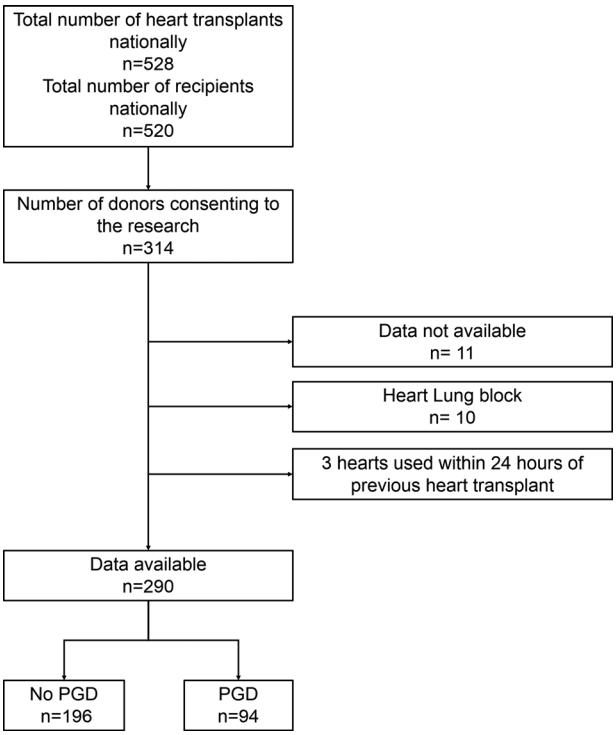

FIGURE 1. Flowchart showing the total number of heart transplants nationally and recruitment to the HEART study.

reported to us for 290 of the 301 transplants (see Figure 1). Of the 290 transplant recipients, 94 developed PGD (32.4%; 95% confidence interval, 27.0% to 38.1%), 8 of whom died within 72 hours from PGF.

Descriptive donor and recipient characteristics of the study cohort are summarized in Table 1.

We evaluated the clinical significance of PGD identified by our definition. Inotropes scores were similar at 6 hours but were significantly higher in the PGD group 24, 48, and 72 hours after transplantation (Table 2). As might be expected, the incidence of prolonged inotropes usage (>72 hours) was higher in the PGD group (75% vs 21%, $P < 0.01$) as was the requirement for an IABP (50% vs 15%, $P < 0.01$), mechanical circulatory support (29% vs 0%, $P < 0.01$), and the incidence of postoperative renal failure requiring replacement therapy (61% vs 26% $P < 0.01$). The median length of intensive care unit stay was longer in the PGD group (14 vs 5 days, $P < 0.01$). The risk of death was almost 4 times greater in the PGD group compared to the non-PGD group (hazard ratio, 3.9; 95% confidence interval, 2.4-6.2; $P < 0.01$; Table 3; Figure 2). When we looked retrospectively at the severity of PGD according to the recently proposed PGD-ISHLT grading system, early mortality was related to PGD severity, PGD-ISHLT grade 3 had the highest mortality, followed by grade 2, whereas the mortality of PGD-ISHLT grade 1 was similar to that of those without PGD (Figure 2). Late mortality in those who survived to discharge was not different in those with or without PGD ($P = 0.81$). Also, ISHLT-PGD grade did not influence postdischarge survival ($P = 0.85$)

DISCUSSION

We found that our prespecified definition of PGD could be applied effectively by the transplant coordinators in the recipient centres and that the identification of PGD was associated with differences in morbidity and mortality. Our overall incidence for PGD was 32%, which is consistent with that reported previously.[17–19,24] The 30-day mortality rate among the PGD population was 37% confirming the mortality reported by others.[22]

When this study was conceived, a standardized definition of PGD had not been established, the consensus from the definitions used in the literature was that PGD is a state of a low CO and raised filling pressures (excluding hypovolemia) after heart transplantation requiring prolonged inotropic support[21,22,45–47] and sometimes mechanical circulatory support where there is no evidence of a technical surgical

TABLE 1.

Donor and recipient characteristics

Donor characteristics	(n = 290)
Age (median [IQR]), y	38 (29–45)
Male sex, n (%)	191 (64%)
Height (median [IQR]), cm	175 (168–182)
Weight (kg) (median (IQR))	75 (70–85)
History, n (%)	
Smoking	143, (48%)
Diabetes	8, (3%)
Hypertension	23, (8%)
Previous CPR, n (%)	42, (14%)
Intubation time (median [IQR]) (n = 272), h	49 (34–88)
Cause of donor death n (%)	
CVA/tumor	197, (66%)
Trauma	39, (13%)
Anoxia	35, (12%)
Infective	5, (2%)
Recipient Characteristics	
Age (median [IQR]), y	43 (24–54)
Male gender, n (%)	191 (64%)
Medical history, n (%)	
Previous cardiac surgery	92 (31%)
Creatinine clearance <50 mL/min	8 (3%)
Antiarrhythmic drugs pretransplant	106 (35%)
Diabetes	20 (7%)
In hospital pretransplant, n (%)	164 (55%)
BMI	24 (21–27)
Pre transplant therapy n (%)	
ECMO	7 (23%)
IABP	29 (10%)
Inotropes	104 (35%)
Ventilated	14 (5%)
Recipient diagnosis n (%)	
IHD	49, 16
DCM	152, 51
Valvular heart disease	5, 2
Congenital heart disease	30, 10
HCM	18, 6
RCM	7, 2
Others	27, 9

Ischemic time: cold ischemic time = time from application of the cross clamp in the donor to arrival in the recipient centre. Warm ischemic time is defined as the time from organ arrival in the recipient centre to reperfusion in the recipient.

PGD, primary graft dysfunction; CVA, cerebrovascular accident; BMI, body mass index; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; CPR, cardiopulmonary resuscitation of any duration for cardiopulmonary arrest; IQR, interquartile range.

TABLE 2.

Inotrope scores in first 72 hours after transplantation

Inotrope score after transplantation (μg/kg per min) (median, IQR)	PGD (n = 94)	No PGD (n = 196)	*P*
6 h	9.44 (4.97–24.1)	8.93 (4.03–16.4)	0.16
24 h	10.7 (5.92–21.6)	5.88 (2.97–15.0)	<0.01
48 h	7.61 (3.08–15.5)	2.51 (0.03–7.36)	<0.01
72 h	5.59 (0.56–15.2)	0.03 (0.00–3.99)	<0.01

complication, including tamponade, or of alloimmune rejection, including hyperacute antibody-mediated rejection.[17,21,22,45,48] The various definitions of PGD used in the literature have resulted in divergent assessments of its impact on survival and complications. Definitions based on inotrope requirements and CO status tend to include a broader spectrum of patients, whereas those restricted to the need for mechanical support or death report a lower incidence and a worse outcome.[19]

Our definition was developed through a consensus between U.K. transplant centers, and its implementation was preceded by education of recipient coordinators, resulting in its standard application. Recipient clinical data in the first 72 hours was collected prospectively solely for the purpose for the study and the transplant recipient coordinators received guidance and access to the core study group using a 24-hour helpline to support accurate data collection.

When this study commenced in 2007, we could not have anticipated the recently proposed definition of PGD by ISHLT (PGD-ISHLT). That definition is conceptually similar to the one used here but it also grades the severity of PGD. The ISHLT group suggested that the definition of primary PGD should be based on left ventricle and right ventricle dysfunction within the first 24 hours with the exclusion of secondary graft dysfunction due to hyper acute rejection, pulmonary hypertension with right ventricle failure, or surgical complication.[44]

We have evaluated prospectively our definition in a national prospective study lasting 4 years and 8 months. To our knowledge, this is the first study to prospectively validate a definition of PGD with multicenter data. Our definition covered the first 72 hours in contrast to PGD-ISHLT which was limited to 24 hours. Because we did not record the specific time point at which PGD was diagnosed within the 72 hours, we are unable to use our data to validate the ISHLT-PGD definition.

The ISHLT group proposed that the use of inotropes be incorporated into their definition. We did not include an inotrope score in our definition but we found that our PGD group had a higher inotrope score and more prolonged use of inotropes, suggesting that the 2 definitions are likely to identify similar patients.

Our study has strengths and limitations. Data were collected nationally in a prospective manner during a period when clinical practices did not change significantly. The number of heart transplants included was large compared with previous studies. The study included all donor hearts from whom consent was obtained, thereby minimizing the risk of selection bias. The criteria and mechanisms for allocation of donor organs, preservation (St Thomas's solution in most of cases) and transportation were standardized and monitored by the Cardiothoracic Transplant Advisory Group, of NHS Blood and Transplant. We believe that PGD is a syndrome that may take more than 24 hours to evolve fully and therefore, the use of data up to 72 hours may have increased the sensitivity of our definition for identifying PGD. Our definition did not rely on echocardiography-derived LVEF, which is sometimes difficult to obtain in the immediate postoperative period and is an operator dependant investigation.

The evaluation of risk factors for PGD was outside the scope of this study. We did not collect raw data on recipient RA pressure, PCWP, pulmonary artery systolic pressure, and echocardiography-derived LVEF at regular intervals during the 72 hours period, this may have reduced the sensitivity of our definition.

The ISHLT group proposed grading PGD based on inotrope score, use of IABP, and mechanical circulatory support. Because of the lack of raw rata on LVEF, RA pressure PCWP, CI on an hourly basis, we could not divide our heart transplant population into those with and without PGD strictly by the proposed ISHLT definition; as a result, we were limited to a modified grading based on inotrope score and mechanical support. We attempted to retrospectively grade our PGD cases in a similar though not identical fashion, we considered the requirement for IABP, VAD (levitronix-like

TABLE 3.

Recipient outcomes by PGD

Recipient outcomes	PGD (n = 94)	No PGD (n = 196)	*P*
Complications, n (%)			
IABP	45/90 (50%)	30/194 (15%)	<0.01
Ventricular assist device(not including ECMO)	25/94 (27%)	0/196 (0%)	<0.01
Prolonged inotrope use >72 h	67/89 (75%)	39/189 (21%)	<0.01
Renal failure requiring renal replacement therapy	55/90 (61%)	50/193 (26%)	<0.01
Return to operating theater (all causes)	51/90 (57%)	38/193 (20%)	<0.01
Length of ICU stay (median, IQR),	14 (6–29)	5 (4–6)	<0.01
Mortality (%, 95% CI)			<0.01
30 d	37.2% (28.3% to 47.8%)	4.1% (2.0% to 8.0%)	
90 d	40.4% (31.3% to 51.1%)	6.1% (3.5% to 10.5%)	
1 y	41.5% (32.3% to 52.1%)	8.2% (5.1% to 13.0%)	
3 y	46.6% (36.6% to 57.8%)	16.5% (11.7% to 22.9%)	

ICU, intensive care unit; 95% CI, 95% confidence interval.

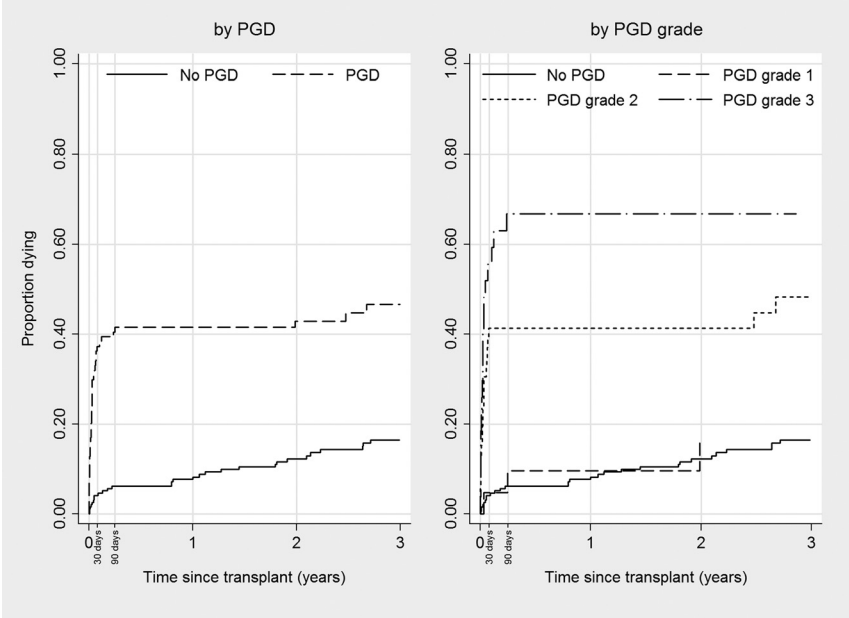

FIGURE 2. Recipient mortality to 3 years by PGD and PGD grade. Grade 1, n = 21; grade 2, n = 46; grade 3, n = 27.

device), ECMO, and calculated the inotrope score in the first 72 hours after transplantation. In this manner, we divided our PGD cohort into grades 1, 2, and 3. We found that a higher PGD grade was associated with increased mortality; however, there were a small number of grade 1 PGD cases (n = 21), and these had a similar mortality rate to the non-PGD recipients (Figure 2).

A clinical definition of PGD should help predict or relate to clinical outcome. Patients meeting our definition of PGD had increased morbidity (return to theatre, renal requirement, and longer intensive therapy unit (ITU) stay). These have been associated with poorer overall outcomes in cardiac surgery. In other studies, the return to theatre for re-sternotomy in cardiac surgery has been shown to be associated with increased mortality, length of ITU stay, inotrope requirements, and morbidity.[49–52] The development of renal failure after cardiac surgery has been demonstrated to be associated with increased mortality and morbidity.[53–58] Further, our PGD cohort had a longer ITU stay which has also been associated with a poorer outcome.[59–61] As a result, PGD has a significant impact on the cost and cost-effectiveness of heart transplantation.

Our robust and easy to apply definition of PGD, which has been prospectively tested and related to outcome may enable clinicians to better assess and identify risk factors for PGD and could provide a suitable endpoint for future studies of donor management, organ protection and matching, and in resource planning. It may also be of use in quality assurance and audit.

In conclusion, our definition of PGD was able to be applied prospectively in a national multicenter study, and the cases it defined had increased mortality, ITU length of stay, and postoperative complications. Our data also support a grading of the severity of PGD similar to that proposed by the ISHLT consensus group.

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REFERENCES

1. Hertz MI, Aurora P, Christie JD, et al. Scientific Registry of the International Society for Heart and Lung Transplantation: introduction to the 2010 annual reports. *J Heart Lung Transplant* 2010;29:1083.
2. Daneshmand MA, Milano CA. Surgical treatments for advanced heart failure. *Surg Clin North Am* 2009;89:967–999, x.
3. de Jonge N, Kirkels JH, Klopping C, et al. Guidelines for heart transplantation *Netherlands Heart J* 2008;16:79.
4. Banner NR, Bonser RS, Clark AL, et al. UK guidelines for referral and assessment of adults for heart transplantation *Heart* 2011;97:1520.
5. Hunt SA. Taking heart–cardiac transplantation past, present, and future. *N Engl J Med* 2006;355:231.
6. Taylor DO, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report–2008. *J Heart Lung Transplant* 2008;27:943.
7. Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City Meeting to maximize the use of organs recovered from the cadaver donor. *Am J Transplant* 2002;2:701.
8. Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J* 2009;30:1771.
9. Goldsmith KA, Demiris N, Gooi JH, et al. Life-years gained by reducing donor heart ischemic times. *Transplantation* 2009;87:243.
10. Khush KK, Valantine HA. New developments in immunosuppressive therapy for heart transplantation *Expert Opin Emerg Drugs* 2009;14:1.
11. Sulemanjee NZ, Merla R, Lick SD, et al. The first year post-heart transplantation: use of immunosuppressive drugs and early complications. *J Cardiovasc Pharmacol Ther* 2008;13:13.
12. Hunt SA, Haddad F. The changing face of heart transplantation. *J Am Coll Cardiol* 2008;52:587.
13. Caves PK, Stinson EB, Graham AF, et al. Percutaneous transvenous endomyocardial biopsy. *JAMA* 1973;225:288.
14. Thomas HL, Dronavalli VB, Parameshwar J, et al. Steering Group of the UK Cardiothoracic Transplant Audit. Incidence and outcome of Levitronix CentriMag support as rescue therapy for early cardiac allograft failure: a United Kingdom national study. *Eur J Cardiothorac Surg* 2011;40:1348.
15. Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report—2007. *J Heart Lung Transplant* 2007;26:769.
16. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult heart transplant report—2009. *J Heart Lung Transplant* 2009;28:1007.
17. Leprince P, Aubert S, Bonnet N, et al. Peripheral extracorporeal membrane oxygenation (ECMO) in patients with posttransplant cardiac graft failure. *Transplant Proc* 2005;37:2879.
18. Ibrahim M, Hendry P, Masters R, et al. Management of acute severe perioperative failure of cardiac allografts: a single-centre experience with a review of the literature. *Can J Cardiol* 2007;23:363.
19. Russo MJ, Iribarne A, Hong KN, et al. Factors associated with primary graft failure after heart transplantation. *Transplantation* 2010;90:444.
20. D'Alessandro C, Golmard JL, Barreda E, et al. Predictive risk factors for primary graft failure requiring temporary extra-corporeal membrane oxygenation support after cardiac transplantation in adults. *Eur J Cardiothorac Surg* 2011;40:962.
21. Lima B, Rajagopal K, Petersen RP, et al. Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. *Circulation* 2006;114:4.
22. Segovia J, Cosio MD, Barcelo JM, et al. RADIAL: a novel primary graft failure risk score in heart transplantation. *J Heart Lung Transplant* 2011;30:644.
23. Young JB, Hauptman PJ, Naftel DC, et al. Determinants of early graft failure following cardiac transplantation, a 10-year, multi-institutional, multivariable analysis. *J Heart Lung Transplant* 2001;20:212.
24. Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-third official adult heart transplantation report–2006. *J Heart Lung Transplant* 2006;25:869.
25. Audibert G, Charpentier C, Seguin-Devaux C, et al. Improvement of donor myocardial function after treatment of autonomic storm during brain death. *Transplantation* 2006;82:1031.
26. el-Abbassi K, Delophont P, Pinelli G, et al. Angiotensin II and endothelin-1 circulating and interstitial myocardial release following brain death. *Transplant Proc* 1996;28:45.
27. Birks EJ, Burton PB, Owen VJ, Latif N, Nyawo B, Yacoub MH. Molecular and cellular mechanisms of donor heart dysfunction. *Transplant Proc* 2001;33:2749.
28. Herijgers P, Leunens V, Tjandra-Maga TB, Mubagwa K, Flameng W. Changes in organ perfusion after brain death in the rat and its relation to circulating catecholamines. *Transplantation* 1996;62:330.
29. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. *Crit Care Med* 1990;18:702.
30. Stoica SC, Satchithananda DK, White PA, Parameshwar J, Redington AN, Large SR. Noradrenaline use in the human donor and relationship with load-independent right ventricular contractility. *Transplantation* 2004; 78:1193.
31. Cushing H. Some experimental and clinical observations concerning states of increased intracranial tension. *Am J Med Sci* 1902;124:373.
32. Banner NR, Thomas HL, Curnow E, et al. The importance of cold and warm cardiac ischemia for survival after heart transplantation. *Transplantation* 2008;86:542.
33. Birks EJ, Yacoub MH, Burton PS, et al. Activation of apoptotic and inflammatory pathways in dysfunctional donor hearts. *Transplantation* 2000;70:1498.
34. Birks EJ, Burton PB, Owen V, et al. Elevated tumor necrosis factor-alpha and interleukin-6 in myocardium and serum of malfunctioning donor hearts. *Circulation* 2000;102:III352.
35. Mudge GH, Goldstein S, Addonizio LJ, et al. 24th Bethesda conference: Cardiac transplantation. Task Force 3: recipient guidelines/prioritization. *J Am Coll Cardiol* 1993;22:21.
36. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. *J Heart Lung Transplant* 1993;12:549.
37. Young JB, Naftel DC, Bourge RC, et al. Matching the heart donor and heart transplant recipient. Clues for successful expansion of the donor pool: a multivariable, multiinstitutional report. The Cardiac Transplant Research Database Group. *J Heart Lung Transplant* 1994; 13:353.
38. Bourge RC, Kirklin JK, Naftel DC, McGiffin DC. Predicting outcome after cardiac transplantations: lessons from the Cardiac Transplant Research Database. *Curr Opin Cardiol* 1997;12:136.
39. Kirklin JK, Naftel DC, Bourge RC, et al. Evolving trends in risk profiles and causes of death after heart transplantation: a ten-year multi-institutional study. *J Thorac Cardiovasc Surg* 2003;125:881.
40. Cardarelli MG, Salim M, Love J, et al. Berlin heart as a bridge to recovery for a failing Fontan. *Ann Thorac Surg* 2009;87.
41. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 2010;11:234.
42. Domico M, Liao P, Anas N, Mink RB. Elevation of brain natriuretic peptide levels in children with septic shock. *Pediatr Crit Care Med* 2008; 9:478.

43. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation* 1995;92:2226.
44. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant* 2014;33:327.
45. Huang J, Trinkaus K, Huddleston CB, Mendeloff EN, Spray TL, Canter CE. Risk factors for primary graft failure after pediatric cardiac transplantation: importance of recipient and donor characteristics. *J Heart Lung Transplant* 2004;23:716.
46. Marasco SF, Esmore DS, Negri J, et al. Early institution of mechanical support improves outcomes in primary cardiac allograft failure. *J Heart Lung Transplant* 2005;24:2037.
47. Marasco SF, Vale M, Pellegrino V, et al. Extracorporeal membrane oxygenation in primary graft failure after heart transplantation. *Ann Thorac Surg* 2010;90:1541.
48. Kavarana MN, Sinha P, Naka Y, Oz MC, Edwards NM. Mechanical support for the failing cardiac allograft: a single-center experience. *J Heart Lung Transplant* 2003;22:542.
49. Charalambous CP, Zipitis CS, Keenan DJ. Chest reexploration in the intensive care unit after cardiac surgery: a safe alternative to returning to the operating theater. *Ann Thorac Surg* 2006;81:191.
50. Karthik S, Grayson AD, McCarron EE, Pullan DM, Desmond MJ. Reexploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. *Ann Thorac Surg* 2004;78:527; discussion 534.
51. Unsworth-White MJ, Herriot A, Valencia O, et al. Resternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. *Ann Thorac Surg* 1995;59:664.
52. Čanádyová J, Zmeko D, Mokráček A. Re-exploration for bleeding or tamponade after cardiac operation. *Interact Cardiovasc Thorac Surg* 2012;14:704.
53. Rosner MH, Okusa MD. Acute Kidney Injury Associated with Cardiac Surgery. *Clin J Am Soc Nephrol* 2006;1:19.
54. Conlon PJ, Stafford-Smith M, White WD, et al. Acute renal failure following cardiac surgery. *Nephrol Dial Transplant* 1999; 14:1158.
55. Ostermann ME, Taube D, Morgan CJ, Evans TW. Acute renal failure following cardiopulmonary bypass: a changing picture. *Intensive Care Med* 2000;26:565.
56. Thakar CV, Worley S, Arrigain S, Yared J-P, Paganini EP. Influence of renal dysfunction on mortality after cardiac surgery: modifying effect of preoperative renal function. *Kidney Int* 2005;67:1112.
57. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardio-thoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; 15:1597.
58. Karkouti K, Wijeysundera DN, Yau TM, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation* 2009; 119:495.
59. Joskowiak D, Kappert U, Matschke K, Tugtekin S. Prolonged intensive care unit stay of patients after cardiac surgery: initial clinical results and follow-up. *Thorac Cardiovasc Surg* 2013;61:701.
60. Hein OV, Birnbaum J, Wernecke K, England M, Konertz W, Spies C. Prolonged intensive care unit stay in cardiac surgery: risk factors and long-term-survival. *Ann Thorac Surg* 2006;81:880.
61. Bashour CA, Yared JP, Ryan TA, et al. Long-term survival and functional capacity in cardiac surgery patients after prolonged intensive care. *Crit Care Med* 2000;28:3847.